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Research Article

A STUDY ON THE ROLE OF METFORMIN IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

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A B S T R A C T

Background: Metformin has been used in Diabetes over prolonged period. We planned this study to evaluate the efficacy of metformin in ADPKD patients at high risk of disease progression.
Materials and methods: This is a single center randomized controlled study with a 2:1 recruitment in intervention and control arm respectively. Patient diagnosed as ADPKD were further stratified according to presence or absence of family history of end stage renal disease before the age of 60 years. Patients with eGFR≤ 45, body mass index ≥30, diabetes were excluded. Metformin was given at 1000mg/day. CT scan was done to assess kidney volumes at baseline and at 1 year. Renal function tests and proteinuria were monitored 3 monthly.
Results: The baseline characteristics were similar in the two groups. The total kidney volumes were 1000.0 ±570.4 ml and 1041.1 ±439.6 ml; and eGFR (estimated glomerular filtration rate) was 82.3±13.2 and 85.1±20.5 ml/min/1.73 m^2 in control and intervention groups respectively. The % change in total kidney volume at one year was significantly lesser in the intervention group compared to control group (p=0.005).
Conclusion: Metformin is a promising alternative in ADPKD to slow the progression of kidney volume which is surrogate maker of progression of kidney disease in ADPKD.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a common monogenic cause of kidney disease and one of the leading causes of end stage renal disease (ESRD) in India[1,2] and also across the world[3]. Enormous progress has been made in elucidating the natural history of disease and the pathogenesis of cyst formation in ADPKD[4,5]. Prospective longitudinal studies have shown that increase in renal volume correlates well with decline in renal function[6,7] both in children[8] and adults[9]. There have been efforts to develop and validate disease specific therapies to slow down the process of growth of cysts and hence retard the progression of kidney disease in ADPKD. While many drugs including tolvaptan and m-tor inhibitors like sirolimus which have significant adverse effects have been tried, therapy with a less expensive drug that can be well-tolerated over a long period of time in patients who are only mildly symptomatic or asymptomatic early in the course of disease continues to be an unmet need in ADPKD. Animal studies have shown that metformin stimulates the energy-sensing molecule AMP-activated protein kinase (AMPK), inhibits the activities of AMPK-dependent cystic fibrosis transmembrane conductance regulator (CFTR) and mammalian target of rapamycin which are one of the key pathogenic pathways in formation and progression of cysts in ADPKD[10,11]. Clinical experience of safety with long term use metformin in patients with normal renal and hepatic function is extensive. We planned this study to investigate the role of metformin, a relatively inexpensive and safe drug in patients with ADPKD.

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MATERIALS AND METHODS

We screened 128 patients of either sex between 18 to 60 years of age diagnosed as ADPKD on ultrasonographic (USG) imaging by unified criteria[12] which states that the presence of three or more (unilateral or bilateral) renal cysts is sufficient for establishing the diagnosis in individuals aged 15 to 39 years and two or more cysts in each kidney is sufficient for individuals aged 40 to 59 years. Those with eGFR (by MDRD formula) ≤ 45 ml/min/1.73 per m^2 , any derangement of liver function tests, other concomitant diseases/conditions that could contribute to decline of renal function like diabetes, obesity (body mass index ≥ 30) were excluded from the study. Patients with uncontrolled hypertension underwent a 3 month observation period during which antihypertensives were titrated and after optimum control of BP they were included in the study. All patients were counselled to maintain a water

intake of 3 to 4 liters/day. Institutional ethics committee approval was obtained prior to enrollment of patients in the study. Patients were randomized into two groups in 2:1 ratio stratified by presence or absence of family history of atleast one member reaching ESRD before 60 years of age. All patients satisfying the above mentioned criteria underwent volumetric analysis of kidneys with CT scan at baseline and at one year. Those with a positive family history were enrolled in the study irrespective of the total kidney volume. Those with no family history were enrolled only if the total kidney volume exceeded 700 ml. All patients in the intervention group received metformin sustained release at the dose of 500 mg/ day which was increased to 1000 mg/day at one month if tolerated. Liver function tests were monitored at 2nd and 4th week and 3 monthly thereafter. Renal function tests, urine examination, hemoglobin were repeated 3 monthly. The serum creatinine level was measured using IDMS-traceable Roche enzymatic method. Patients who stopped medication for≥ 3 weeks for any reason were excluded from final analysis.

RESULTS

A total of 60 patients completed the study. Of these, 20 patients were in control arm and 40 in the intervention arm as shown in figure 1. The baseline characteristics in the two groups were similar as shown in table 1 and table 2. The average BP in the control and intervention groups was 130 ± 6 and 134 ± 4 mm of Hg respectively. The percentage change in eGFR, proteinuria and individual as well as total kidney volumes was calculated. The statistical analysis was carried out with IBM SPSS Version-20. Categorical data was presented as actual numbers and percentages. For normally distributed data, with-in group analysis was performed by using paired "t" test and between group analyses by unpaired "t" test. Non-normally distributed data was analyzed by using non-parametric "Mann-Whitney U test". Categorical variables were analyzed with "Fischer's exact test". All the efficacy parameters were presented as absolute change from baseline. A negative sign indicates decrease and vice versa. For statistical significance, a two tailed probability value of less than 0.05 was considered.

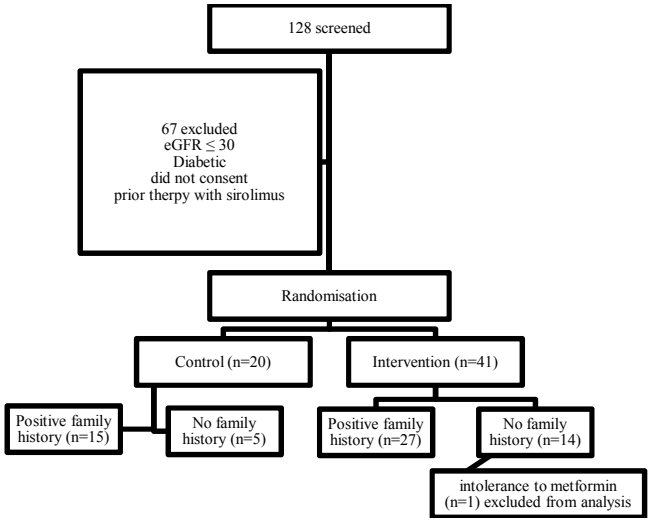

Figure 1 Flowchart of patient enrollment and inclusion in analysis

Table 1 Comparison of baseline characteristics

Parameters		Group				P Value
		Control (n=20)		Intervention (n=40)		
		n	%	n	%	
Gender	Female	11	55.0%	20	50.0%	0.72
	Male	9	45.0%	20	50.0%	
Family H/O	No	5	25.0%	13	32.5%	0.55
	Yes	15	75.0%	27	67.5%	
Hypertension	No	7	35.0%	24	60.0%	0.06
	Yes	13	65.0%	16	40.0%	
No. Antihypertensive drugs	0	7	35.0%	24	60.0%	0.03
	1	12	60.0%	9	22.5%	
	2	1	5.0%	6	15.0%	
	3	0	0.0%	1	2.5%	

Table 2 Comparison of baseline characteristics

Parameters	Group				P Value
	Control (n=20)		Intervention (n=40)		
	Mean	SD	Mean	SD	
Age(yrs)	38.6	8.7	38.9	8.4	0.87
eGFR Baseline (ml/min/1.73m2)	82.3	13.2	85.1	20.5	0.57
Protein Baseline (mg/24 hr)	141.4	237.1	249.1	209.4	0.09
Right Kidney Volume Baseline (ml)	506.9	332.7	513.9	220.4	0.93
Left Kidney Volume Baseline (ml)	493.1	255.7	527.3	242.6	0.62
Total kidney Volume Baseline (ml)	1,000.0	570.4	1,041.1	439.6	0.77

Counselling to maintain water intake 3 to 4 lit/day was emphasized at each visit in all patients. Water driven lowering of AVP (arginine vasopressin) decreases cAMP and cyst generation. One patient could not tolerate the minimum dose of metformin 500m/day and was excluded from the final analysis. 2 patients (5%) had diarrhea and nausea on increasing dose of metformin from 500mg/d to 1000mg/day and subsequently were continued on 500mg/day dose for the rest of the study period. Those who tolerated metformin 1000mg/day were continued on that dose till the end of the study. None of the patients had any serious adverse effects. None had derangement of liver function tests requiring discontinuation of metformin.

Mild symptoms related to ADPKD like pain in abdomen were not different in the two groups and there was non-significant decrease (p=0.25) in the intervention group. Severe symptoms like cyst hemorrhage, gross hematuria and cyst infection were comparable in the two groups at baseline and did not differ significantly on follow up (n=1 in each group). None of the patients required hospital admission. There was a significantly lesser increase in individual as well as total kidney volumes in the intervention group compared to the control group (p values have been shown in table 3).

Table 3 Change in parameters after one year of follow up

Parameters	Group				P Value
	Control (n=20)		Intervention (n=40)		
	Mean	SD	Mean	SD	
% change eGFR from baseline	-6.5	17.7	-7.3	21.7	0.89
% change proteinuria from baseline	38.1	150.1	-5.7	52.5	0.12
% change Right KV* from baseline	12.6	12.1	1.0	15.8	0.005
% change Left KV from baseline	14.7	17.8	3.0	17.6	0.02
% change Total KV from baseline	13.0	11.1	1.6	15.3	0.005

*KV: kidney volume

The percentage change in total kidney volume has been shown in figure 2. However, the percentage change in eGFR (by MDRD) and 24 hour proteinuria was not significant.

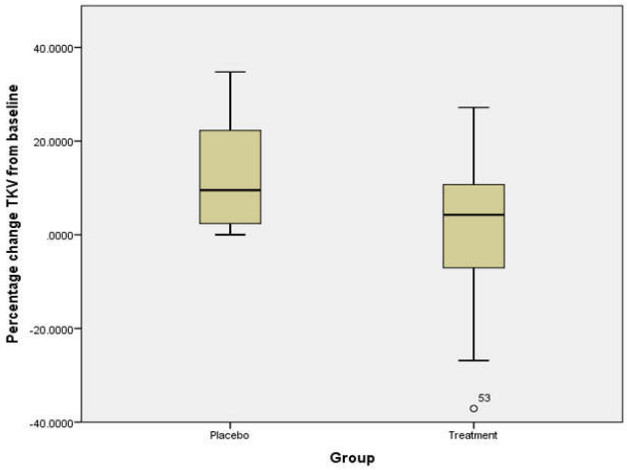

Figure 2

DISCUSSION

In patients with ADPKD, the decline in GFR occurs much later in the course of the disease[9]. As the initial kidney volume and increase in kidney volumes over time correlates with decline in renal function over long term follow up, these parameters have been used as surrogate markers to study the effectiveness of drugs in halting or slowing the disease progression in ADPKD[13,14]. Metformin seems to be an economical and attractive therapeutic strategy considering the animal studies that have shown stimulation of AMPK by metformin to influence downstream effects and slow cystogenesis in ADPKD[5,10]. The risk of disease progression is variable in ADPKD. Genotyping helps in identifying the high risk mutations but these are not routinely available especially in developing countries as of now. However, family history may predict the possible gene mutations involved and hence the risk of rapid disease progression in ADPKD[15]. Therefore, in this study those patients who had family history of at least one member having ESRD before 60 years of age were considered high risk and included in the study irrespective of their baseline total kidney volume especially because metformin is a safer drug compared to the other drugs that have been tried in ADPKD like sirolimus and tolvaptan. Another major risk factor indicating progressive disease is a large baseline total kidney volume. This group of patients has been included in drug trials in ADPKD with unknown genetics[13]. Hence, in those without family history and with total kidney volume >700 ml were considered for inclusion in our study.

We found significantly lesser increase in individual and total kidney volumes in those patients who received metformin compared to those who did not. However, the change in eGFR was insignificant. As the disease progresses slowly over decades in ADPKD short follow up of one year is unlikely to show any improvement in terms of GFR or delay in onset of ESRD. An extended follow up of this cohort is being continued to analyze the long term effects.

There was no significant decrease in ADPKD related symptoms like pain in abdomen, cyst hemorrhage, gross hematuria or cyst infection in the intervention group; however the overall numbers were too small. This could be because the total kidney volume of patients in our study was much lower than that included in other studies[13].

Relatively small number of patients and short follow up are the major limitations of this study.

CONCLUSION

Metformin is a promising alternative for disease specific therapy in ADPKD especially in terms of reduction in total kidney volume. It may have beneficial effects on symptoms related to increasing kidney sizes in ADPKD. The validation of the effect of metformin on kidney sizes as well as its long term impact on renal function needs to be further studied.

Conflict of interest: None to declare

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